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CYTYC CORPORATION
250 CAMPUS DRIVE
MARLBOROUGH, MA 01752

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/410,336
Filing Date: October 01, 1999
Appellant(s): LOVE ET AL.

Theodore R. Allen
For Appellant

3-05

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 15, 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is essentially correct, but for the following, which is noted for clarity.

The ground of rejection under 35 U.S.C. § 103(a) set forth in section 15 of the FINAL Office action mailed September 23, 2004 cites U.S. Patent No. 4,628,027 A as a relied upon reference. Although cited in the first paragraph of the rejection, there is no further discussion of the reference in the stated ground of rejection that follows that first paragraph. The inclusion of the citation of U.S. Patent No. 4,628,027 A in this ground of rejection was an inadvertent error, as the prior art reference has not been considered, or relied upon in determining the obviousness of the claimed invention.

Accordingly, the second issue (i.e., Issue 2) is whether under 35 U.S.C. § 103(a), claims 34 and 35 are unpatentable over Yoshimoto et al. in view of U.S. Patent No. 5,681,543 A and Canto et al., as applied to claims 33 and 36-39 in the ground of rejection identified as "Issue 1", and in further view of U.S. Patent No. 6,168,779 B1.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 33 and 36-39 and claims 34 and 35 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,681,543 A	SCHMITT-WILLICH	10-1997
6,168,779 B1	BARSKY	1-2001

Canto MIF, et al. "Methylene blue selectively stains intestinal metaplasia in Barrett's esophagus". Gastrointestinal Endoscopy. Vol. 44, No. 1 (1996), pp. 1-7.

Yoshimoto M, et al. "Magnetic resonance galactography for a patient with nipple discharge". Breast Cancer Research and Treatment. Vol. 42 (1997), pp. 87-90.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

"Issue 1". Claims 33 and 36-39 are rejected under 35 U.S.C. § 103(a). This rejection is set forth in section 14 of the prior FINAL Office Action, which was mailed on September 23, 2004.

The following is a reiteration of this ground of rejection:

Claims 33 and 36-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Yoshimoto et al. (*Breast Cancer Res. Treat.* **42**: 87-90, 1997) in view of

US Patent No. 5,681,543 A, and Canto et al. (*Gastrointestinal Endoscopy* **44**: 1-7, 1996).

Claims 33 and 36-39 are drawn to a method of identifying the location of breast cancer cells within a breast duct or breast ductal network comprising delivering a compound comprising a targeting molecule coupled to an identifying agent into the breast duct, allowing the compound to specifically bind at least one breast cancer cell within the breast duct or breast ductal network, washing the breast duct and breast ductal network with a solution to remove nonspecifically bound compound, detecting the presence of the bound compound within the breast duct or breast ductal network, and identifying the location of the breast cancer cells to which the compound is bound within the breast duct or breast ductal network.

Yoshimoto et al. teaches a method of identifying the location of a lesion of breast cancer cells within a breast duct or breast ductal network for the purpose of excising the lesion and surrounding tissue comprising delivering a compound comprising an identifying agent into the breast duct, allowing the compound to specifically bind such a lesion within the breast duct or breast ductal network, detecting the presence of the bound compound within the breast duct or breast ductal network, and identifying the location of the lesion to which the compound is bound within the breast duct or breast ductal network by magnetic resonance imaging of the patient's torso; see the entire document.

More particularly, Yoshimoto et al. teaches a method for diagnosing a primary lesion of breast cancer cells and assessing its spread within the breast by magnetic

resonance galactography comprising injecting gadolinium-DTPA directly into a discharging breast duct and performing magnetic resonance imaging (MRI) of the breast of the supine patient before and after infusion of gadolinium-DTPA by rapid intravenous injection before surgery to remove the lesion and as little of the surrounding tissue as possible and practical; see the entire document (e.g., the abstract; page 87, columns 1 and 2; and page 90, column 1). Yoshimoto et al. teaches, because planar images are acquired while the patient is supine, the methodology provides useful information to supplement that acquired using conventional methodology (e.g., mammography), particularly since when using mammography to localize lesions within the breast, it is hard to judge the exact location or spread of the lesions because the images are acquired while the breast is compressed; see, e.g., the abstract and page 87, column 1. Yoshimoto et al. teaches their methodology enables the clinician to determine the location of the lesion within the breast while the patient is supine, as the patient would be during surgery, so the images acquired may provide the surgeon with more useful information prior to conservative surgery (i.e., the resection of the lesion and as little of the surrounding tissue as possible and practically necessary) than images acquired by conventional methodology alone; see, e.g., page 87, column 1, and page 90, columns 1 and 2.

However, Yoshimoto et al. does not teach delivering a compound comprising an identifying agent coupled to a targeting agent (claim 33), wherein said targeting agent is selected from the group consisting of a protein, an antibody, an antibody fragment, a polynucleotide, a small molecule, a liposome, a ligand, a peptide, and a receptor (claim

34). Furthermore, Yoshimoto et al. does not teach washing the breast duct into which the compound is injected to remove non-specifically bound compound (claim 34).

US Patent No. 5,681,543 A ('543) teaches identifying agents coupled to targeting agents (e.g., an antibody, small molecule, or ligand that selectively targets tumor cells) for use in identifying the location of lesions within the breast by, for example, magnetic resonance imaging; see the entire document.

More particularly, '543 teaches gadolinium-containing polymer complexes, which exhibit surprisingly high tissue specificity and, as compared to gadolinium-DTPA, are more stable and provide marked contrast enhancement of peripheral tumor tissue by nuclear magnetic imaging for a prolonged period, bringing a marked diagnostic gain; see entire document (e.g., column 8, lines 19-26 and lines 44-52). '543 teaches the gadolinium-containing polymer complexes can be covalently attached to a biomolecule or a macromolecule, which concentrates in the organ or organ part to be examined, such as an enzyme, hormone, dextran, porphyrin, bleomycin, insulin, prostaglandin, steroid hormone, amino sugar, amino acid, peptide, protein, monoclonal antibody, lectin, lipid, or liposome (column 13, lines 25-34). '543 teaches such conjugates of monoclonal antibodies specific for tumor-associated antigens are suitable for use in tumor diagnosis (column 13, lines 34-42). '543 teaches for visualization of tumors, monoclonal antibodies or their antigen-binding fragments (e.g., Fab and $F(ab')_2$), which are specific for human tumors of the breast are suitable (column 13, lines 48-57). '543 teaches that conjugates of antibodies and the gadolinium-containing polymer complexes can be produced without loss or reduction of the binding affinity and

specificity of the antibody for the antigen; see, e.g., column 14, lines 25-28. '543 teaches the conjugates can be formulated as pharmaceutical agents, which are suitable for use as contrast media for nuclear magnetic resonance imaging or MRI (nuclear spin tomography); see, e.g., column 17, lines 59-62; and column 61 and 62, Example 66.

Canto et al. teaches an endoscopic procedure comprising an *in vivo* washing step before identifying the location of tumor tissue within a patient's body. The procedure for localizing tumor tissue in a patient's body comprises contacting the tissue and surrounding area with an identifying agent, allowing the identifying agent to bind to the cells of the tissue, washing off the excess of an identifying agent, and localizing the tumor tissue so identified; see entire document (e.g., page 2, paragraph bridging columns 1 and 2).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to identify the location of lesions within a breast duct or breast ductal network for the purpose of conservatively excising the lesion and surrounding tissue by a process according to claims 33 and 36-39 because: (a) Yoshimoto et al. teaches the injection of gadolinium-DPTA into the breast duct to identify the location of such lesions by magnetic resonance imaging for the purposes of excising the lesions and surrounding tissue by conservative surgery; (b) '543 teaches gadolinium-containing polymer complexes, which can be used more effectively than gadolinium-DTPA; (c) '543 teaches or suggests that the targeted delivery of gadolinium using a diagnostic compound comprising a gadolinium-containing polymer complex and a targeting agent can be performed advantageously, since a targeted identifying agent

targeted to lesions in the breast duct or breast ductal network concentrate in breast duct or breast ductal network and specifically bind lesions of the breast; and (d) Canto et al. teaches or suggests that washing to remove non-specific bound diagnostic agents can be performed by *in vivo* endoscopic procedures to improve the specificity of the test by reducing background noise, or the generation of non-specific, undesired signals.

One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to identify the location of such lesions a breast duct by magnetic resonance imaging for the purposes of excising the lesions and surrounding tissue by conservative surgery.

"Issue 2". Claims 34 and 35 are rejected under 35 U.S.C. § 103(a). This rejection is set forth in section 15 of the prior FINAL Office Action, which was mailed on September 23, 2004.

The following is a reiteration of this ground of rejection:

Claims 34 and 35 rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshimoto et al. (*Breast Cancer Res. Treat.* **42**: 87-90, 1997) in view of US Patent No. 5,681,543 A and Canto et al. (*Gastrointestinal Endoscopy* **44**: 1-7, 1996) as applied to claims 33 and 36-39 above, and further in view of US Patent No. 6,168,779 B1.

Claim 34 is drawn to the method of claim 33 wherein the compound is delivered by non-percutaneous cannulation or catheterization of the breast, where the term "non-

percutaneous" describes cannulation or catheterization without piercing or perforating the skin. Claim 34 is drawn to the method of claims 33 wherein the compound is delivered to more than one duct on a breast.

Yoshimoto et al., US Patent No. 6,168,779 B1, US Patent No. 4,628,027 A, and Canto et al. teach that which is set forth above.

However, none of Yoshimoto et al., US Patent No. 6,168,779 B1, US Patent No. 4,628,027 A, and Canto et al. expressly teach that the compound comprising the identifying agent coupled to a targeting agent can be delivered by non-percutaneous cannulation or catheterization of the breast without piercing or perforating the skin (claim 34); nor do any of Yoshimoto et al., US Patent No. 6,168,779 B1, US Patent No. 4,628,027 A, and Canto et al. expressly teach or suggest delivering the compound to more than one breast duct (claim 35).

US Patent No. 6,168,779 B1 ('779) teaches delivering a desired diagnostic material through one or more orifices at the surface of the breast and into the lumens of the associated breast ducts by cannulation or catheterization without piercing or perforating the skin; see entire document (e.g., column 6, lines 54-55).

In addition, '779 teaches the cytologic analysis of nipple discharge from a breast can be used diagnostically to evaluate whether breast cancer exists within the discharging duct; however, '779 teaches, because the fluid is generally collected at the surface of the nipple, the fluid is representative of the entire ductal structure and the analysis does not generally provide information on the condition of an individual duct (column 1, lines 29-42). '779 teaches, since breast cancer usually arises from a single

ductal system and exists in a precancerous state for a number of years, endoscopy in and fluid collection from individual breast ducts has great diagnostic potential for identification of intermediate markers of premalignant and malignant breast cancer lesions within the breast duct and breast ductal network; see, e.g., column 1, lines 17-62. '779 teaches the diagnostic potential of such methods cannot be realized until access to each and every duct in a patient's breast can be assured (column 1, lines 43-49). To facilitate this process, '779 teaches a method for locating and labeling an orifice at the surface of a breast into the lumen of a breast duct; see the entire document (e.g., the abstract; and column 1, lines 12-16). '779 teaches, by reliably identifying each of such orifice, all the ductal networks within the breast can be located and subsequently accessed for diagnostic purposes; see, e.g., column 1, lines 57-62; and column 2, lines 37-43. '779 teaches the introduction of suitable diagnostic materials, such as contrast medium, into the breast ducts prior to imaging for the purpose of localizing cancerous lesions of the breast duct epithelium have been previously described by others (e.g., Sartorius, *Breast Cancer Res. Treat.* **35**: 255-266, 1995); see, e.g., column 1, line 64, through column 2, line 31. Furthermore, '779 teaches saline can be instilled into the lumen of the breast duct through a catheter to wash and/or dilate the lumen, which is then aspirated through the same catheter or another cannula; and the cells contained in the aspirated saline washings may be collected, spun down, and identified by histopathological analysis; see, e.g., column 6, lines 37-65.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to deliver the compound according to claim 34, because '779

teaches the disclosed methods comprising cannulation or catheterization of one or all of the individual breast ducts provide a means by which a desired diagnostic material can be instilled through one or more orifices at the surface of the breast and into the lumens of the associated breast ducts.

Furthermore, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to identify, access, and deliver, to more than one breast duct according to claim 35, because '779 teaches methods for identifying each of the orifices at the surface of the breast duct associated with a breast duct and suggests the importance of evaluating the presence of lesions in each individual breast duct, not only the discharging duct, since breast cancer usually arises from a single ductal system and exists in a precancerous state for a number of years.

One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to identify the location of lesions in one or more breast ducts or breast ductal networks by magnetic resonance imaging for the purposes of excising the lesions and surrounding tissue by conservative surgery and otherwise clinically intervening in the course of the disease as soon as possible and as deemed appropriate following the localization of any precancerous lesions.

Furthermore, because '779 teaches aspirated saline washings of the ductal lumen may be collected for further diagnostic use, one ordinarily skilled in the art at the time the invention was made would have been motivated to wash the lumen both to remove non-specifically bound targeting agent before image acquisition and to collect cells for additional diagnostic use.

(11) Response to Argument

"Issue 1"

At page 4 of the Brief, Appellant has asserted that the Examiner has incorrectly argued that nonobviousness cannot be shown by attacking references individually where the rejections are base upon combinations of references. Appellant's assertion is noted, but as the claims are in fact rejected under 35 U.S.C. § 103(a) over a combination of references, as opposed to any individual reference. As stated at page 4 of the Advisory Action mailed February 2, 2005, and notably contrary to Appellant's assertion, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As an apparent basis for their assertion, Appellant has cited *In re Royka and Martin*, 180 USPQ 580 (CCPA 1974). *Royka* is not believed pertinent to this issue, as the decision there indicates that to support an anticipatory rejection, all elements of claim must be found in the reference, and in instances where an element of the claim is missing, the addition of other references would still not make the invention obvious. This is not the case here. All elements of the claims are taught or suggested by the combination of the references cited as the basis of the rejection; and as such, attacking the cited prior art references for their individual deficiencies, rather than as a whole, cannot be relied upon to establish nonobviousness over the whole. Moreover, in deciding *Merck*, the Federal Circuit indicated that each reference "must be read, not in

isolation, but for what it fairly teaches in combination with the prior art as a whole" *Id.* at p. 380.

Then, at page 4, Appellant proceeds to traverse the ground of rejection, arguing the individual deficiencies of Yoshimoto et al. Appellant has asserted that Yoshimoto et al. does not teach or suggest a method for identifying the location of a lesion within the breast or breast ductal network. To the contrary, Yoshimoto et al. does in fact teach magnetic resonance galactography for imaging, and thereby identifying the location of, a lesion of breast cancer cells in the breast duct of a patient; see, e.g. the title of the reference, the abstract, the introduction (page 87, column 1), and Figure 2 (page 89). At page 90, column 1, Yohimoto et al. discloses that following pathologic examination of the mastectomized tissue, it was confirmed that the location of the wide-spread comedo carcinoma of mainly ductal carcinoma *in situ* coincided with the location of the lesion shown by MR galactography (Figure 2, page 89), which, in essence, is "proof-of-principle" that MR galactography may be used to pinpoint the exact location of such lesions in the breast of patients. Accordingly, contrary to Appellant's argument that the claimed invention would not have been obvious because of the alleged deficiency of Yoshimoto et al., Yoshimoto et al. teaches a method for identifying the location of a lesion within the breast or breast ductal network.

Beginning at page 4 (paragraph 4) of the Brief, Appellant has further asserted that not only is Yoshimoto et al. deficient but that Yoshimoto et al. teaches away from the claimed invention. Appellant has noted that in reference to Figure 1, at page 88, Yoshimoto et al. discloses, "it is difficult to know the exact location of the disease within

the breast from these images" (Figure 1, accompanying figure legend). The images to which Yoshimoto et al. refers in the accompanying figure legend are of course the images depicted in the figure. The images depicted in Figure 1 are images that were generated by either mammography (Figure 1 (A)) or galactography (Figure 1 (B)). In contrast to the images depicted in Figure 1, the images depicted in Figure 2, which unlike the images depicted in Figure 1 pinpoint the location and extent of the lesion within the breast, were generated using the newly disclosed method of magnetic resonance galactography. In fact, Yoshimoto et al. pointedly discloses that this new method was developed in order to specifically overcome the problems encountered in accurately judging the location or spread of lesions using images acquired by conventional mammography and galactography, as exemplified by Figure 1, which are caused by compression of the breast of the supine patient during the imaging procedure; see page 88, column 1. Accordingly, contrary to Appellant's assertion, Yoshimoto et al. most assuredly does not teach away from the claimed invention and it is again submitted that Appellant has manipulatively taken the referred to statement of Yoshimoto et al. out of context to support their assertion.

At page 5, Appellant has further asserted that Yoshimoto et al. is deficient in teaching or suggesting a method for identifying the specific location of a lesion within the breast duct or breast ductal network. If by use of the word "specific", Appellant has intended to argue that the prior art is deficient in teaching a method for identifying the exact location of the breast cancer cells, notably the claims are not directed to a method for identifying the *specific or exact* location of breast cancer cells within the breast.

Nevertheless, as discussed above, at page 90, column 1, Yohimoto et al. discloses that following pathologic examination of the mastectomized tissue, it was confirmed that the location of the wide-spread comedo carcinoma of mainly ductal carcinoma *in situ* coincided with the location of the lesion shown by MR galactography (Figure 2, page 89). Therefore, despite Appellant's assertion that Yoshimoto et al., "at best", teaches a combination of more than one galactographic method may provide more useful information about intraductal lesions in patients with nipple discharge, the disclosure of Yoshimoto et al. is "proof-of-principle" that MR galactography may be used to pinpoint the exact location of such lesions in the breast of patients. Therefore, the fact that Yoshimoto et al. suggests that combining their newly developed method with other conventional methods may provide yet additional information regarding the patient's lesions does not support Appellant's assertion that the individual reference is somehow deficient, or that the claimed invention would not be obvious over the whole of the prior art.

Then, beginning at page 5, Appellant continues to traverse the ground of rejection, arguing the individual deficiencies of U.S. Patent No. 5,681,543 A. In particular, Appellant has argued that the patent is deficient in teaching or suggesting the use of the disclosed magnetic resonance imaging agents for identifying the specific location of lesions within the breast, as Appellant has noted that there is but one mention of breast cancer in the specification, and then only in relation to antibodies specific for such lesions, which may be conjugated to the disclosed gadolinium-containing polymer complexes, such that the complexes are specifically targeted to

such lesions. In response to what appears to be an argument that there would be no reason to combine the cited references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as clearly noted in the ground of rejection reiterated above, the patent teaches conjugates of monoclonal antibodies specific for tumor-associated antigens and the disclosed gadolinium-containing polymer complexes are suitable for use in tumor diagnosis (column 13, lines 34-42) and visualization of tumors, including tumors of the breast (column 13, lines 48-57). Moreover, the patent teaches the conjugates can be produced without loss or reduction of the binding affinity and specificity of the antibody for the antigen (column 14, lines 25-28) and can be formulated as pharmaceutical agents, which are suitable for use as contrast media for nuclear magnetic resonance imaging or MRI (nuclear spin tomography) (column 17, lines 59-62; and column 61 and 62, Example 66). Accordingly, despite the fact that Yoshimoto et al. does not teach delivering a compound comprising an identifying agent coupled to a targeting agent, as recited in claim 33, wherein said targeting agent is selected from the group consisting of a protein, an antibody, an antibody fragment, a polynucleotide, a small molecule, a liposome, a ligand, a peptide, and a receptor, as further limited by claim 34, the patent teaches identifying agents coupled to targeting agents (e.g., an antibody, small

molecule, or ligand that selectively targets tumor cells) for use in identifying the location of lesions within the breast by, for example, magnetic resonance imaging. Therefore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to identify the location of lesions of breast cancer cells within a breast duct or breast ductal network for the purpose of conservatively excising the lesion and surrounding tissue by a process, as claimed, because: (a) Yoshimoto et al. teaches the injection of gadolinium-DPTA into the breast duct to identify the location of such lesions by magnetic resonance imaging for the purposes of excising the lesions and surrounding tissue by conservative surgery; (b) the patent teaches gadolinium-containing polymer complexes, which can be used more effectively than gadolinium-DTPA; and (c) the patent teaches or suggests that the targeted delivery of gadolinium using a diagnostic compound comprising a gadolinium-containing polymer complex and a targeting agent can be performed advantageously, since a targeted identifying agent targeted to lesions in the breast duct or breast ductal network concentrate in breast duct or breast ductal network and specifically bind lesions of the breast. Then, given the obviousness of the claimed invention in view of the cited combination of prior art, one ordinarily skilled in the art at the time the invention was made would have been motivated to do so to identify the location of such lesions a breast duct by magnetic resonance imaging for the purposes of excising the lesions and surrounding tissue by conservative surgery.

Then, beginning at page 6, Appellant continues to traverse the ground of rejection, arguing the individual deficiencies of Canto et al. In particular Appellant has

argued that Canto et al. is deficient in teaching or suggesting *in vivo* washing during endoscopic procedures to remove non-specific bound diagnostic agents and thereby increase the specificity of a diagnostic test. Washing non-specifically bound detectable reagents to increase the specificity of diagnostic tests is not a new or inventive concept, as such steps were then conventional, routine, and obvious, particularly in instances where the detectable reagents used may adhere non-specifically and unwantedly to cells and tissue, since logically the presence of such non-specifically bound reagents will preclude or obscure detection of the location of the specifically-bound reagent. If the diagnostic procedure is an endoscopic procedure, which is performed *in vivo*, the necessarily the step of washing must be performed *in vivo*. Contrary to Appellant's assertion, Canto et al. specifically teaches endoscopic diagnostic procedures, which do in fact include such "washing" steps by which excess or non-specifically bound reagents are removed to thereby increase the specificity of the diagnostic test; see, e.g., page 2, column 2.

Appellant has argued "the washing step described by Canto *et al.* can not be used to improve the specificity of the test by reducing the generation of non-specific, undesired signals because methylene blue does not stain specifically" (page 7, paragraph 2) and further argued that Canto et al. is somehow deficient, since "there is nothing in Canto *et al.* suggests that methylene blue would selectively stain breast cancer cells in a breast duct" (page 7, paragraph 2). In reply, the claims are not directed to a method comprising selectively staining breast cancer cells in a breast duct with methylene blue. Rather, the claims are directed to a method comprising washing

the breast duct and breast ductal network with a solution to remove nonspecifically bound compound before detecting the presence of the bound compound within the breast duct or breast ductal network to identify the location of the breast cancer cells to which the compound is bound within the breast duct or breast ductal network. Yoshimoto et al. teaches a method of identifying the location of a lesion of breast cancer cells within a breast duct or breast ductal network for the purpose of excising the lesion and surrounding tissue comprising delivering a compound comprising an identifying agent into the breast duct, allowing the compound to specifically bind such a lesion within the breast duct or breast ductal network, detecting the presence of the bound compound within the breast duct or breast ductal network, and identifying the location of the lesion to which the compound is bound within the breast duct or breast ductal network by magnetic resonance imaging of the patient's torso. However, Yoshimoto et al. does not teach washing the breast duct into which the compound is injected to remove non-specifically bound compound. Canto et al. teaches an endoscopic procedure comprising an *in vivo* washing step to remove the excess of an identifying agent before identifying the location of tumor tissue within a patient's body. Accordingly, despite the apparent deficiency of Yoshimoto et al., it would have been obvious to one ordinarily skilled in the art at the time the invention was made to identify the location of lesions within a breast duct or breast ductal network for the purpose of conservatively excising the lesion and surrounding tissue by a process that includes a step in which excess or non-specifically bound identifying compound is removed because Canto et al. teaches or suggests that washing to remove excess or non-

specifically bound diagnostic agents is performed *in vivo* during endoscopic procedures, which, given the routine and conventional inclusion of such "washing" steps in diagnostic procedures in general, would have been understood to suggest that such steps improve the specificity of the test by reducing background noise, or the generation of non-specific, undesired signals.

Beginning at page 8, Appellant has argued that there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one ordinarily skilled in the art, to modify the references or combine their teachings. This argument is largely addressed by the above response to Appellant's earlier arguments. Contrary to Appellant's assertion, there is suggestion and motivation, both in the references themselves and in the knowledge generally available to one ordinarily skilled in the art, to modify the method disclosed by Yoshimoto et al. in accordance with the teachings of both the U.S. Patent No. 5,681,543 A and Canto et al. to practice the Appellant's disclosed invention, as claimed, to identify the specific location of breast cancer cells within the breast duct or breast ductal network for the purpose of excising the lesion by surgical resection. Again, Yoshimoto et al. provides "proof-of-principle" that MR galactography may be used to pinpoint the exact location of such lesions in the breast of patients. Moreover, Yoshimoto et al. teaches that their method overcomes limitations of more conventional diagnostic techniques to afford better, more precise determinations of the specific location of the lesions in the breasts of patients. Although Yoshimoto et al. does not expressly teach conjugating the gadolinium-containing diagnostic reagent used in MR galactography to a anti-tumor targeting agent, such as

an antibody that binds an antigen displayed at the surface of the tumor cells, U.S. Patent No. 5,681,543 A teaches gadolinium-containing diagnostic imaging reagents, which are detected by magnetic resonance and which are conjugated to anti-tumor targeting agents, such as antibodies that binds antigens displayed at the surface of the tumor cells, which bind selectively to such tumors to more precisely pinpoint their exact location in the body. Furthermore, although Yoshimoto et al. does not teach washing the breast duct into which the compound is injected to remove non-specifically bound compound, Canto et al. teaches an endoscopic procedure comprising an *in vivo* washing step to remove the excess of an identifying agent before identifying the location of tumor tissue within a patient's body, which would have been understood to suggest that such steps, which were routine and conventional, improve the specificity of the test by reducing background noise, or the generation of non-specific, undesired signals to permit more precise detection of specifically-bound diagnostic reagent and therefore enable a more exact determination of the location of the lesion within the body.

At page 12, Appellant has argued that at most, the cited prior art would merely set forth an "obvious to try" rationale in support of this obviousness rejection. In support of this assertion, Appellant has cited *In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995). While it is agreed that in deciding Deuel, the Federal Circuit expressed agreement with earlier decisions that "[o]bvious to try has long been held not to constitute obviousness", further explaining that "[a] general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out" *Id.* at p. 1216. However, in this instance, as opposed to that, the claims are drawn to a

method for identifying the location of breast cancer cells within a breast, where the prior art (i.e., Yoshimoto et al.) provides "proof-of-principle" that MR galactography may be used to pinpoint the exact location of such lesions in the breast of patients. As such, it is submitted that it is unreasonable to assert that the prior art merely provides a rationale to try to practice the disclosed invention, as claimed, because it has already been established that such an approach can be used. Again, Yoshimoto et al. teaches identifying the location of breast cancer cells in the breast of a patient using MR galactography and although Yoshimoto et al. does not teach the gadolinium-containing diagnostic imaging reagent can targeted to the cancer cells by conjugation to a targeting moiety, such as an anti-tumor antibody, U.S. Patent No. 5,681,543 A teaches gadolinium-containing diagnostic imaging reagents, which are commonly detected by magnetic resonance and which are conjugated to anti-tumor targeting agents, such as anti-tumor antibodies, which bind selectively to breast cancer cells in the breast to enable the artisan to more precisely pinpoint their exact location in the breast. In contrast, the Federal Circuit, in deciding *Deuel*, indicated that it would only have been possible to try to isolate a specific DNA molecule encoding an isolated protein, since the degeneracy of the genetic code prevents the artisan from knowing for certain that just such a DNA molecule exists and can in fact be isolated. Here, both Yoshimoto et al. and U.S. Patent No. 5,681,543 A teach gadolinium-containing diagnostic imaging reagents, which are detected by magnetic resonance, and both reference disclose that the reagents can be used to precisely pinpoint the exact location of breast cancer cells in the body. Therefore, unlike the situation in *Deuel*, here, there is no apparent, sound

scientific reason that the artisan could not reasonably expect to successfully practice the claimed invention, given benefit of the combined teachings of the prior art.

Then, beginning at page 13, Appellant has traversed this ground of rejection, arguing just the contrary, namely that there would have been no reasonable expectation of success. In particular, Appellant has argued that none of the cited prior art references teach targeting moieties that bind selectively to breast cancer cells in the breast duct or breast ductal network. However, as should be immediately evident, given the discussion above, this assertion is unfounded. U.S. Patent No. 5,681,543 A teaches gadolinium-containing diagnostic imaging reagents, which are detected by magnetic resonance, which are conjugated to targeting moieties that bind selectively to tumor cells (e.g., an antibody that binds an antigen displayed at the surface of tumor cells), which U.S. Patent No. 5,681,543 A teaches is used to precisely pinpoint the exact location of breast cancer cells in the body.

At page 13, Appellant has further argued that there would be no expectation that the washing step would successfully remove non-specifically bound dye in the breast duct because methylene blue does not bind specifically to breast cancer cells. Again, the claims are not directed to a method comprising staining breast cancer cells in the breast duct with methylene blue; but in response to the apparent assertion that the claims are directed to an imaging agent that binds specifically, as opposed to non-specifically, if the imaging agent binds only specifically, why does the claimed invention comprise a step in which non-specifically bound imaging agent is removed by washing? It is thus submitted that Appellant's arguments are contradictory and paradoxical.

Nonetheless, as Canto et al. suggests, it was routine and conventional at the time of the invention to wash excess and non-specifically bound detectable reagents before acquiring the image by detecting the reagent, since logically the presence of excess and non-specifically bound reagents would preclude or obscure the detection of specifically-bound reagent. Moreover, Canto et al. teaches that such a step is performed *in vivo* during endoscopic procedures, which are akin to the claimed invention, at least inasmuch as the claimed invention is performed using a catheter, which may be fitted with an endoscope. If there is some sound scientific reason that one ordinarily skilled in the art would not have had a reasonable expectation of successfully removing non-specifically bound reagent in practicing the claimed invention by washing the breast duct or breast ductal network, then, that reason eludes discovery; and notably, Appellant has not proffered such reasoning to support such an assertion.

"Issue 2"

At page 15, Appellant has again argued the Examiner has incorrectly argued that nonobviousness cannot be shown by attacking references individually where the rejections are base upon combinations of references. The merit of this argument has already been addressed.

Then, beginning at page 16, Appellant proceeds to traverse the ground of rejection, arguing the individual deficiency of U.S. Patent No. 6,168,779 B1. Appellant has asserted that U.S. Patent No. 6,168,779 B1 does not teach or suggest a method for identifying the specific location of cancer cells within a breast duct or breast ductal

network. In response, because none of Yoshimoto et al., U.S. Patent No. 6,168,779 B1, and Canto et al. expressly teaches that the compound comprising the identifying agent coupled to a targeting agent is delivered by non-percutaneous cannulation or catheterization of more than one breast duct without piercing or perforating the skin, U.S. Patent No. 6,168,779 B1 ('779) is cited as teaching just such a delivery of a desired diagnostic material (see, e.g., column 6, lines 54-55). In addition, U.S. Patent No. 6,168,779 B1 teaches the cytologic analysis of nipple discharge from a breast can be used diagnostically to evaluate whether breast cancer exists within the discharging duct; however, because the fluid is generally collected at the surface of the nipple, the fluid is representative of the entire ductal structure and the analysis does not generally provide information on the condition of an individual duct (column 1, lines 29-42). U.S. Patent No. 6,168,779 B1 teaches, since breast cancer usually arises from a single ductal system and exists in a precancerous state for a number of years, endoscopy in and fluid collection from individual breast ducts has great diagnostic potential for identification of intermediate markers of premalignant and malignant breast cancer lesions within the breast duct and breast ductal network; see, e.g., column 1, lines 17-62. U.S. Patent No. 6,168,779 B1 teaches the diagnostic potential of such methods cannot be realized until access to each and every duct in a patient's breast can be assured (column 1, lines 43-49). To facilitate this process, U.S. Patent No. 6,168,779 B1 teaches a method for locating and labeling an orifice at the surface of a breast into the lumen of a breast duct; see the entire document (e.g., the abstract; and column 1, lines 12-16). U.S. Patent No. 6,168,779 B1 teaches, by reliably identifying each of such

orifice, all the ductal networks within the breast can be located and subsequently accessed for diagnostic purposes; see, e.g., column 1, lines 57-62; and column 2, lines 37-43. U.S. Patent No. 6,168,779 B1 teaches the introduction of suitable diagnostic materials, such as contrast medium, into the breast ducts prior to imaging for the purpose of localizing cancerous lesions of the breast duct epithelium have been previously described by others (e.g., Sartorius, *Breast Cancer Res. Treat.* **35**: 255-266, 1995); see, e.g., column 1, line 64, through column 2, line 31. Finally, U.S. Patent No. 6,168,779 B1 teaches saline can be instilled into the lumen of the breast duct through a catheter to wash and/or dilate the lumen, which is then aspirated through the same catheter or another cannula; and the cells contained in the aspirated saline washings may be collected, spun down, and identified by histopathological analysis; see, e.g., column 6, lines 37-65.

In combination, therefore, the prior art would have made the disclosed invention, as claimed, obvious, in particular, because U.S. Patent No. 6,168,779 B1 teaches the disclosed methods comprising cannulation or catheterization of one or all of the individual breast ducts provide a means by which a desired diagnostic material is instilled through one or more orifices at the surface of the breast and into the lumens of the associated breast ducts. Given the obviousness of the claimed invention, one ordinarily skilled in the art at the time the invention was made would have been motivated to practice the claimed invention to identify the location of lesions in one or more breast ducts or breast ductal networks by magnetic resonance imaging for the purposes of excising the lesions and surrounding tissue by conservative surgery and

otherwise clinically intervening in the course of the disease as soon as possible and as deemed appropriate following the localization of any precancerous lesions.

Furthermore, because '779 teaches aspirated saline washings of the ductal lumen may be collected for further diagnostic use, one ordinarily skilled in the art at the time the invention was made would have been motivated to wash the lumen both to remove non-specifically bound targeting agent before image acquisition and to collect cells for additional diagnostic use.

Then, beginning at page 18 and proceeding through to the top of page 22, Appellant has reiterated the arguments that there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to artisans of ordinary skill, to modify or combine the teachings of the references, that at best, there would have only been an "obvious to try rationale, and that there would have been no reasonable expectation of success. It is believed that the merit of each of these arguments has been already addressed, as these same arguments were raised in Appellant's traversal of "Issue 1" and the reasons that Appellant's arguments are not persuasive are essentially the same.

Appellant is reminded that the test for obviousness is not whether the features of the secondary references may be bodily incorporated into the structure of the primary references; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Furthermore, because Appellant has argued repeatedly argued that the references fail to show intentionally practicing the claimed process to identify the specific location of breast cancer cells, it is noted that such features are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Even so, the term "specific location" has not been defined in the specification. So, while it cannot be determined if by such an argument Appellant has asserted that the invention determines the exact location of the breast cancer cells within the breast duct or breast ductal network, it also cannot be determined how such a feature, if it were recited in the claims, would be considered to distinguish the claimed invention from that process that would have been obvious in light of the combination of the prior art, since, again, Yoshimoto et al. teaches a method for pinpointing the exact (i.e., specific) location of breast cancer cells within the breast.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
June 20, 2005

Conferees:

Jeffrey Siew
Supervisory Patent Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
6/22/05

James Housel
Supervisor Patent Examiner
Art Unit 1648

JAMES HOUSEL 6/22/05
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

CYTYC CORPORATION
250 CAMPUS DRIVE
MARLBOROUGH, MA 01752